Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Materials Table of Contents

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Table S1: Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Age 6 months to 85 years
2) Able to complete the informed consent process or, if a minor, a parent or guardian who is able to complete the informed consent process; an assent form also will be completed for children age 7 and older
3) Willing and able to complete the study protocol, study-related activities, and visits
4) Diagnosis of uSSSI, either cellulitis (defined as an inflammation of skin and associated skin structures) or abscess (defined as a circumscribed collection of pus), evidenced by at least 2 of the following localized signs or symptoms on the skin for at least 24 hours:
    a. Erythema
    b. Swelling or induration
    c. Local warmth
    d. Purulent drainage
    e. Tenderness to palpation or pain
5) Able to take oral antibiotic therapy, either in pill or suspension form.

Exclusion Criteria:

1) Hospital in-patient
2) Hospitalization within the prior 14 days
3) Residence in a long-term skilled nursing facility
4) Requirement for hospitalization for skin infection or other condition
5) Previous enrollment in this protocol
6) Participation in another clinical trial within the previous 30 days
7) Superficial skin infection only, including
    a. Impetigo
    b. Ecthyma
    c. Folliculitis

d. Infections that have a high cure rate after surgical incision alone (such as isolated furunculosis) or after topical or local measures

8) Unstable psychiatric or psychological condition rendering the subject unlikely to be cooperative or to complete study requirements
9) Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with the adherence or subject compliance with study requirements
10) Systolic blood pressure > 180 mm Hg
11) Systolic blood pressure (SBP) less than an age-specific critical value:
    a. Age 6 -11 months: < 70 mm Hg
    b. Age 1 to 8 years: < 80 mm Hg
    c. Age 9 to 17 years: < 90 mm Hg
    d. Age $\geq$ 18 years: < 90 mm Hg
12) Heart rate less than 45 beats per minute (BPM)
13) Heart rate greater than an age-specific critical value:
    a. Age 6 -11 months: > 140 BPM
    b. Age 1 to 8 years: > 120 BPM
    c. Age 9 to 17 years: > 120 BPM
    d. Age $\geq$ 18 years: > 120 BPM.
14) Oral temperature (or equivalent rectal, tympanic membrane, axillary defined in Table 2) less than 35.5° C (95.9° F)
15) Oral temperature (or equivalent rectal, tympanic membrane, axillary defined in Table 2) greater than age-specific critical value:
    a. Age 6 -11 months: > 38.0° C (100.4° F)
    b. Age 1 to 8 years: > 38.5° C (101.3° F)
    c. Age 9 to 17 years: > 38.5° C (101.3° F)
    d. Age $\geq$ 18 years: > 38.5° C (101.3° F).
16) Documented human or witnessed animal bite in the past 30 days at the site of infection
17) Systemic antibacterial therapy with antistaphylococcal activity within the prior 14 days.

18) The following concomitant medications: warfarin, phenytoin, methotrexate., rosiglitazone or sulfonylureas and systemically administered antibacterial agents with activity against staphylococci
19) Diagnosed or suspected disseminated or severe *S. aureus* or GAS infection, including lymphangitic spread of skin infection, septicemia, bacteremia, pneumonia, endocarditis, osteomyelitis, septic arthritis, gangrene, necrotizing fasciitis, myositis, or other serious or infections
20) Infection at an anatomical site skin requiring specialized management or specialized antimicrobial therapy, including
    a. Periauricular or orbital infection
    b. Perirectal infection
    c. Suspected deep space infection of the hand or foot
    d. Genital infection
    e. Mastitis
    f. Bursitis
21) Radiographic evidence or suspicion of gas in the tissue or foreign body infection (note: radiography is *not* required for screening and can be performed at the discretion of the treating physician)
22) Gastrointestinal symptoms such as nausea, vomiting, or diarrhea of a severity that would preclude consumption of oral antibiotics
23) Hypersensitivity or history of allergic reaction to study drug
24) History of G6PD deficiency
25) Third trimester pregnancy: pregnant women must have gestational age estimated by an objective means, e.g. ultrasound, fundal height, and women who are within 4 weeks of the third trimester of pregnancy, defined as week 27 of pregnancy, are not eligible.
26) Currently breast feeding
27) Severe or morbid obesity with a body mass index (BMI) >40 kg/m^2
28) Complicated skin or soft tissue infection, such as
    a. Catheter or catheter site infection within 30 days of placement
    b. Surgical site infection

c. Known or suspected prosthetic device infection
d. Suspected Gram-negative or anaerobic pathogen
e. Unusual exposure history (e.g., underwater injury, fish-tank exposure, heavy soil exposure, etc)
f. Infection at the site of an area of underlying skin disease such as chronic eczema, psoriasis, atopic dermatitis, or chronic venous stasis

29) History of underlying immunocompromising condition or immunodeficiency, for example
a. Diabetes mellitus
b. Chronic renal failure, creatinine clearance <30 ml/min
c. Renal dialysis within the past 180 days
d. HIV-positive with either CD4 count <200 or <4% CD4 in the past 180 days *or* HIV-positive and no documented CD4 count in the past 4 months
e. Organ or bone marrow transplantation (ever), immunosuppressive therapy within the past 180 days, severe liver disease

Other serious underlying disease, as determined by the treating physician or the investigator

Table S2: Preparation and dosing of clindamycin (at 25 to 30 mg/kg/day) and trimethoprim-sulfamethoxazole (at 8 to 10 mg of trimethoprim/kg/day) suspension, based on weight

Clindamycin

Weight (kg)	Low End (ml/dose)	High End (ml/dose)	Volume (ml) of 15 mg/ml stock suspension to be used for final suspension, TID dosing	Volume (ml) of sterile water to formulate final suspension	Volume (ml) of final suspension to be administered, TID dosing
5-5.4	2.8-3.0	3.3-3.6	3	2	5
5.5-6.0	3.1-3.3	3.7-4.0	3.5	1.5	5
6.1-7.0	3.4-3.9	4.1-4.7	4	1	5
7.1-8.0	3.9-4.4	4.7-5.3	4.5	0.5	5
8.1-9.0	4.5-5.0	5.4-6.0	5	0	5
9.1-10	5.1-5.6	6.1-6.7	6	4	10
10.1-11.5	5.6-6.4	6.7-7.7	6.5	3.5	10
11.6-13	6.4-7.2	7.7-8.7	7.5	2.5	10
13.1-15	7.3-8.3	8.7-10	8.5	1.5	10
15.1-18	8.4-10.0	10.1-12.0	10	0	10
18.1-20	10.1-11.1	12.1-13.3	12	3	15
20.1-23	11.2-12.8	13.4-15.3	13	2	15
23.1-27	12.8-15.0	15.4-18.0	15	0	15
27.1-30	15.1-16.7	18.1-20	18	2	20
>30	16.7	20.1	20	0	20

Trimethoprim-sulfamethoxazole

Weight (kg)	Low End (ml/dose)	High End (ml/dose)	Volume (ml) of 8 mg/ml stock suspension to be used for final suspension, BID dosing	Volume (ml) of inert diluent to formulate final suspension	Volume (ml) of final suspension to be administered, BID dosing
5-6	2.5-3.0	3.1-3.8	3	2	5
6.1-7.0	3.1-3.5	3.8-4.4	3.5	1.5	5
7.1-8.0	3.6-4.0	4.4-5.0	4	1	5
8.1-10	4.1-5.0	5.1-6.3	5	0	5
10.1-12	5.1-6.0	6.3-7.5	6	4	10
12.1-15	6.1-7.5	7.6-9.4	7.5	2.5	10
15.1-18	7.6-9.0	9.4-11.3	9	1	10
18.1-20	9.1-10	11.3-12.5	10	0	10
20.1-25	10.1-12.5	12.6-15.6	12.5	2.5	15
25.1-30	12.6-15	15.7-18.8	15	0	15
30.1-35	15.1-17.5	18.8-21.9	17.5	2.5	20
>35	17.6	21.9	20	0	20

Table S3: Demographics: Gender, Ethnicity, Race and Age by Treatment

	Therapy		
	Clindamycin (N=264)	**TMP/SMX (N=260)**	**All Therapies (N=524)**
Gender - n (%)			
Male	135 (51.1)	139 (53.5)	274 (52.3)
Female	129 (48.9)	121 (46.5)	250 (47.7)
Ethnicity - n(%)			
Non-Hispanic or Non-Latino	188 (71.2)	186 (71.5)	374 (71.4)
Hispanic or Latino	76 (28.8)	74 (28.5)	150 (28.6)
Race - n(%)			
American Indian/Alaskan Native	1 (0.4)	2 (0.8)	3 (0.6)
Asian	5 (1.9)	4 (1.5)	9 (1.7)
Hawaiian/Pacific Islander	4 (1.5)	2 (0.8)	6 (1.1)
Black/African American	141 (53.4)	138 (53.1)	279 (53.2)
White	102 (38.6)	109 (41.9)	211 (40.3)
Multi-Racial	10 (3.8)	4 (1.5)	14 (2.7)
Other/Unknown	1 (0.4)	1 (0.4)	2 (0.4)
Age (Years)			
Mean (SD)	26.8 (17.2)	27.5 (16.9)	27.1 (17.0)
Median	26.0	27.0	26.0
Min, Max	(0, 75)	(0, 67)	(0, 75)
Age Group - n(%)			
<1 Years - n(%)	6 (2.3)	5 (1.9)	11 (2.1)
1-8 Years - n(%)	45 (17.0)	42 (16.2)	87 (16.6)
9-17 Years - n(%)	30 (11.4)	27 (10.4)	57 (10.9)
>=18 - n(%)	183 (69.3)	186 (71.5)	369 (70.4)

	Clindamycin (N=264)	TMP/SMX (N=260)	All Therapies (N=524)
Temperature (°C)*			
Mean (SD)	36.61 (0.50)	36.59 (0.52)	36.60 (0.51)
Median	36.60	36.60	36.60
Min, Max	(35.5, 38.1)	(35.3, 38.3)	(35.3, 38.3)
Location of Wound, n (%)*			
Head/Neck	16 (6.1)	21 (8.1)	37 (7.1)
Trunk/Abdomen/Back	36 (13.6)	41 (15.8)	77 (14.7)
Groin/Buttocks	65 (24.6)	52 (20.0)	117 (22.3)
Upper Extremity	73 (27.7)	61 (23.5)	134 (25.6)
Lower Extremity	73 (27.7)	84 (32.3)	157 (30.0)
Area of Wound (cm^2)* ‡			
n	263	259	522
Mean (SD)	43.84 (140.03)	35.35 (71.13)	39.62 (111.28)
Median	5.89	9.42	7.07
Min, Max	(0.0, 1366.6)	(0.0, 546.6)	(0.0, 1366.6)
q1-q3 (IQR)	2.2 - 23.6 (21.4)	3.1 - 28.3 (25.1)	2.4 - 25.5 (23.2)
Incision and Drainage Performed, n (%)	122 (46.2)	111 (42.7)	233 (44.5)
Erythema, n (%)*	243 (92.0)	237 (91.2)	480 (91.6)
Swelling or Induration, n (%)*	258 (97.7)	246 (94.6)	504 (96.2)
Local Warmth, n (%)*	251 (95.1)	246 (94.6)	497 (94.8)
Purulent Drainage, n (%)*	124 (47.0)	113 (43.5)	237 (45.2)
Tenderness or Pain, n (%)*	261 (98.9)	252 (96.9)	513 (97.9)

	Clindamycin (N=264)	TMP/SMX (N=260)	All Therapies (N=524)
Primary Wound Classification			
Number of Lesions			
1, n (%)*	170 (64.4)	174 (66.9)	344 (65.6)
2, n (%)*	57 (21.6)	51 (19.6)	108 (20.6)
3, n (%)*	15 (5.7)	15 (5.8)	30 (5.7)
4 or more, n (%)*	21 (8.0)	19 (7.3)	40 (7.6)
Type of lesion¶			
Abscess only, n (%)*	80 (30.3)	80 (30.8)	160 (30.5)
Cellulitis only, n (%)*	136 (51.5)	144 (55.4)	280 (53.4)
Mixed** abscess/cellulitis, n (%)*	47 (17.8)	35 (13.5)	82 (15.6)
Not characterized	1 (0.4)	1 (0.4)	2 (0.4)

Table S3 Legend:

This table is a more detailed version of Table 1 and includes data shown and not shown in Table 1.

Note: p-values for all comparisons were non-significant (p>0.05 for all comparisons)

Denominator for percentages is the number of subjects in the intention to treat population for each group.

*Denominator was n=263 for clindamycin and n=259 for TMP/SMX for these characteristics.

‡ Areas were calculated using formula for an ellipse (length*width*pi/4).

**Mixed abscess/cellulitis lesions are subjects with >1 lesion who had at least one abscess lesion that underwent incision and drainage and at least one cellulitis lesion that did not require incision and drainage.

¶ Unknown lesion in 2 subjects

Table S4: Microbiologic results stratified by cellulitis without abscess and abscess subgroups.

A. Summary of Wound Culture by Species at Baseline - Cellulitis Only, Intent-to-Treat Population

	Therapy		
Primary Wound Species	**Clindamycin (N=136) n (%)**	**TMP/SMX (N=144) n (%)**	**All Therapies (N=280) n (%)**
Staphylococcus species			
MRSA	17 (12.5)	15 (10.4)	32 (11.4)
MSSA	4 (2.9)	6 (4.2)	10 (3.6)
Coagulase-negative staphylococcus	7 (5.1)	7 (4.9)	14 (5.0)
Streptococcus species			
Group A streptococcus	-	1 (0.7)	1 (0.4)
Group B streptococcus	1 (0.7)	-	1 (0.4)
Viridans group streptococcus	-	1 (0.7)	1 (0.4)
Alpha-hemolytic streptococcus	-	1 (0.7)	1 (0.4)
Other Species			
Diphtheroid bacilli	1 (0.7)	1 (0.7)	2 (0.7)
Enterobacter species	1 (0.7)	-	1 (0.4)
Other	2 (1.5)	1 (0.7)	3 (1.1)
No Culture Obtained	108 (79.4)	116 (80.6)	224 (80.0)

B. Summary of Wound Culture by Species at Baseline - Abscess Only, Intent-to-Treat Population

	Therapy		
Primary Wound Species	**Clindamycin (N=80) n (%)**	**TMP/SMX (N=80) n (%)**	**All Therapies (N=160) n (%)**
Staphylococcus species			
MRSA	42 (52.5)	47 (58.8)	89 (55.6)
MSSA	9 (11.3)	12 (15.0)	21 (13.1)
Coagulase-negative staphylococcus	9 (11.3)	10 (12.5)	19 (11.9)
Streptococcus species			
Group A streptococcus	2 (2.5)	2 (2.5)	4 (2.5)
Group B streptococcus	-	1 (1.3)	1 (0.6)
Beta-hemolytic group C streptococcus	1 (1.3)	-	1 (0.6)
Beta-hemolytic group F streptococcus	-	1 (1.3)	1 (0.6)
Viridans group streptococcus	5 (6.3)	5 (6.3)	10 (6.3)
Alpha-hemolytic streptococcus	1 (1.3)	1 (1.3)	2 (1.3)
Other Species			
Diphtheroid bacilli	7 (8.8)	5 (6.3)	12 (7.5)
Escherichia coli	1 (1.3)	2 (2.5)	3 (1.9)
Haemophilus species	1 (1.3)	2 (2.5)	3 (1.9)
Klebsiella species	-	2 (2.5)	2 (1.3)
Proteus mirabilis	8 (10.0)	1 (1.3)	9 (5.6)
Bacterial growth NOS	1 (1.3)	-	1 (0.6)
Other	7 (8.8)	6 (7.5)	13 (8.1)
Culture Obtained but No Growth	3 (3.8)	4 (5.0)	7 (4.4)
Culture Obtained but No Results	3 (3.8)	1 (1.3)	4 (2.5)
No Culture Obtained	1 (1.3)	1 (1.3)	2 (1.3)

C. Summary of Wound Culture by Species at Baseline - Mixed Abscess/Cellulitis Lesions, Intent-to-Treat Population

	Therapy		
Primary Wound Species	Clindamycin (N=47) n (%)	TMP/SMX (N=35) n (%)	All Therapies (N=82) n (%)
Staphylococcus species			
MRSA	32 (68.1)	25 (71.4)	57 (69.5)
MSSA	5 (10.6)	4 (11.4)	9 (11.0)
Coagulase-negative staphylococcus	3 (6.4)	2 (5.7)	5 (6.1)
Streptococcus species			
Group A streptococcus	1 (2.1)	2 (5.7)	3 (6.4)
Beta-hemolytic group C streptococcus	1 (2.1)	-	1 (1.2)
Non-group A and B beta-hemolytic streptococcus	1 (2.1)	-	1 (1.2)
Viridans group streptococcus	3 (6.4)	-	3 (3.7)
Alpha-hemolytic streptococcus	-	1 (2.9)	1 (1.2)
Other Species			
Diphtheroid bacilli	-	1 (2.9)	1 (1.2)
Enterococcus species	1 (2.1)	1 (2.9)	2 (2.4)
Escherichia coli	1 (2.1)	-	1 (1.2)
Haemophilus species	1 (2.1)	-	1 (1.2)
Klebsiella species	1 (2.1)	-	1 (1.2)
Lactobacillus species	2 (4.3)	-	2 (2.4)
Proteus mirabilis	1 (2.1)	-	1 (1.2)
Bacterial growth NOS	1 (2.1)	-	1 (1.2)
Other	2 (4.3)	-	2 (2.4)
Culture Obtained but No Growth	3 (6.4)	2 (5.7)	5 (6.1)
Culture Obtained but No Results	1 (2.1)	2 (5.7)	3 (3.7)

Supplemental Table 5: Adverse Treatment Events among the Safety Population

	Clindamycin (n, %)	TMP-SMX (n,%)
Gastrointestinal disorders	34 (13.1)	37 (14.3)
Abdominal pain	1 (0.4)	3 (1.2)
Constipation	1 (0.4)	0 (0.0)
Diarrhea	25 (9.7)	26 (10.1)
Haematochezia	1 (0.4)	0 (0.0)
Nausea	6 (2.3)	7 (2.7)
Vomiting	6 (2.3)	4 (1.6)
Dyspepsia	0 (0.0)	1 (0.4)
Frequent bowel movements	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	8 (3.1)	6 (2.3)
Dermatitis, diaper	1 (0.4)	0 (0.0)
Erythema	1 (0.4)	0 (0.0)
Pruritus	4 (1.5)	3 (1.2)
Rash	3 (1.2)	2 (0.8)
Rash, papular	0 (0.0)	1 (0.4)
Nervous system disorders	7 (2.7)	5 (1.9)
Dizziness	3 (1.2)	3 (1.2)
Headache	3 (1.2)	3 (1.2)
Somnolence	1 (0.4)	0 (0.0)
Infections and infestations	4 (1.5)	3 (1.2)
Cellulitis	1 (0.4)	0 (0.0)
Fungal infection	2 (0.8)	2 (0.8)
Fungal vulvovaginal infection	1 (0.4)	1 (0.4)

General disorders and administration site conditions	3 (1.2)	6 (2.3)
Fatigue	1 (0.4)	2 (0.8)
Pyrexia	2 (0.8)	3 (1.2)
Pain	0 (0.0)	1 (0.4)
Irritability	0 (0.0)	1 (0.4)
Cardiac disorders	1 (0.4)	0 (0.0)
Tachycardia	1 (0.4)	0 (0.0)
Vascular disorders	1 (0.4)	0 (0.0)
Hot flush	1 (0.4)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)
Lymphadenopathy	0 (0.0)	1 (0.4)
Total	**49 (18.9)**	**48 (18.6)**

Table S5 Legend

Supplemental adverse events were tabulated from the Safety Population, defined as those subjects for who took at 1 or more doses of study medication (clindamycin, n=259 and TMP-SMX, n= 258)

Table S6: Summary of Adverse Events by Severity and Relationship to Treatment, Safety Population

Treatment Group=Clindamycin								
				Severity‡				
Relatedness	**Subjects Experiencing an AE N(%)***	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life-Threatening N(%)**	**Death N(%)**
Yes	49 (18.9)	68	0	43 (37.1)	10 (8.6)	0	0	0
No	84 (32.4)	129	4 (3.4)	52 (44.8)	41 (35.3)	2 (1.7)	0	0
Total	116 (44.8)	197	4 (3.4)	85 (73.3)	49 (42.2)	2 (1.7)	0	0

Treatment Group=TMP/SMX								
				Severity‡				
Relatedness	**Subjects Experiencing an AE N(%)***	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life-Threatening N(%)**	**Death N(%)**
Yes	48 (18.6)	68	0	39 (29.5)	11 (8.3)	0	0	0
No	108 (41.9)	160	5 (3.8)	64 (48.5)	54 (40.9)	6 (4.5)	0	0
Total	132 (51.2)	228	5 (3.8)	88 (66.7)	59 (44.7)	6 (4.5)	0	0

Table S6 Legend

Safety population defined as those subjects took at 1 or more doses of study medication (clindamycin, n=259 and TMP-SMX, n= 258)

* Denominator for percentages is the number of subjects in the safety population.

‡ Denominator for percentages is the number of subjects with an adverse event.

Table S7: Treatment Discontinuation and Breakdown of Failures in the Intent to Treat Population

	Clindamycin N (%)	**TMP/SMX N (%)**	**All Therapies N (%)**
Total Randomized	264	260	524
Did not receive drug	5 (2)	2 (1)	7 (1)
Received drug	259 (98)	258 (99)	517 (98)
Excluded from Efficacy at TOC visit	22 (8)	29 (11)	51 (10)
Reason for Exclusion:			
Lost to follow up	9 (3)	18 (7)	27 (5)
Voluntary withdrawal	8 (3)	3 (1)	11 (2)
Withdrawal by investigator	1 (0.4)	0 (0)	1 (0.2)
Non-compliance with protocol/protocol violation	2 (1)	0 (0)	2 (0.4)
Missed TOC visit	1 (0.4)	6 (2)	7 (1)
Terminated due to AEs	0 (0)	2 (1)	2 (0.4)
Took non-study antibiotic	1 (0.4)	0 (0)	1 (0.2)
Cured at TOC visit	212 (80)	202 (78)	414 (79)
Failed at TOC visit	52 (20)	58 (22)	110 (21)
"Administrative" failures	27 (10)	31 (12)	58 (11)
Non-administrative (treatment) failures	25 (9)	27 (10)	52 (10)

Table S7 Legend

Abbreviations
TOC = Test of Cure

“Administrative failures” defined as patients who did not receive drug plus those excluded from exclusion of efficacy at TOC visit.

Non-administrative failures defined as: lack of resolution of signs or symptoms the SSSI at TOC visit, occurrence of an SSSI at a new body site, unplanned surgical treatment of the SSSI, or hospitalization related to the SSSI